Author's response to reviews

Title: Regional Anesthesia and Lipid Resuscitation for Local Anesthetic Systemic Toxicity in China: Results of a Survey by the Orthopedic Anesthesia Group of the Chinese Society of Anesthesiology

Authors:

Mao Xu (anae@163.com)
Shanliang Jin (biyy657@hotmail.com)
Zhengqian Li (lizhengqianmazui@126.com)
Xuzhong Xu (xuzhong@236.net)
Xiuli Wang (wangxi301@aliyun.com)
Lan Zhang (zlzxm@163.com)
Zeguo Feng (Beijing_301@sina.com)
Buwei Yu (yubuwei_2013@126.com)
Jin Liu (scujiinliu@foxmail.com)
Xiangyang Guo (puthmzk@163.com)

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Author's response to reviews: see over
Dear Dr. Hisham Hosny,

Thank you very much for giving us the opportunity to revise my article entitled “Regional Anesthesia and Lipid Resuscitation for Local Anesthetic Systemic Toxicity in China: Results of a Survey by the Orthopedic Anesthesia Group of the Chinese Society of Anesthesiology” (MS:1499011659169303). We have revised the manuscript carefully according to your and the reviewers’ insightful suggestions and advice. We also thank the two reviewers for their excellent comments and suggestions regarding our paper, and we truly appreciate the considerable time and effort expended on their part to improve the paper. We believe the paper has been further improved.

Here are my specific responses to the reviewers:

**Respond to Reviewer # 1’s comments**

- Major Compulsory Revisions: none
- Minor Essential Revisions: none
- Discretionary Revisions: none

  **Response:** none

**Respond to Reviewer # 2’s comments**

Major compulsory comments:

1. The 23 item questionnaire should be included in the article and acknowledgement to authors who developed the original questionnaires should be declared with copyright to publish.

  **Response:** Thanks. The 23 item questionnaire has been added in Appendix 1.

2. Use of confidence interval and odd's ratio is more informative.

  **Response:** A confidence interval has be used to describe the data in Table 1.

Minor essential comments:

1. In figure (1), the summation of all percentages exceeded 100%.
Response: Because there were 5 (14%) responding departments selected multiple drugs as the preferred anesthetics, the summation of all percentages exceeded 100% (Figure 1). We have explained this point in line 144-147, page 7 in the revised manuscript.

(2) In figure (3), the label of the whole figure was missed.

Response: The label of the figure 3 has been added.

(3) In line (70), it's better to say (not widely used) than to say (widely unavailable).

Response: We have made the suggested change.

(4) spelling mistakes and wrong use of terms:

In line (54), practice instead of practices.

In line (112), ethical committee in stead of ethics committee.

In line (128), a p value instead of P.

In line (148), 7 instead of seven.

In lines (149, 150, 151), institutions instead of institution.

In line (150), 7 instead of seven.

Inline(173), eight institutions instead of eight.

In line(189), reported instead of reporting.

In line(223), intravascular injection instead of vascular.

In line(227), reduction instead of reductions.

Response: Thanks for your careful reading. I have revised all of above points according to your suggestion and comments.

Discretionary comments:

(1) The level of training and experience of anesthesiologist who performed PNBs is better to be mentioned.

Response: The level of training and experience of anesthesiologist who performed PNBs has been added in line 151-154, page 7.

(2) The dosages of local anesthetics used was not mentioned and it is better to mention it.

Response: Unfortunately, questions about the dosages of local anesthetics used was not
included in this questionnaire. So data bout the dosages of local anesthetics were not available at this time.

(3) It's better to clarify which guidelines the eight centers had preferred to use??

(AAGBI, AHA, ASRA,.................................................................).

Response: The guidelines the eight centers had preferred to use has been clarified in line 184-186, page 9.

**Respond to Reviewer # 3’s comments**

The author is introducing an interesting subject about the availability and the incidence of the use of lipid emulsion rescue therapy in the treatment of local anesthetic systemic toxicity, however the following comments must be considered:

1- Page 1 row 2-4: Please make the font of the title unified (all bold and not italic).

Response: We have made the suggested change.

2- Page 1 row 11: please correct "affliated" into "affiliated".

Response: We have made the suggested change.

3- Page 3 row 47: please start the words of "local anesthetic systemic toxicity" with capital letters to be "Local Anesthetic Systemic Toxicity", this would be more appropriate to denote the abbreviation mentioned afterwards.

Response: We have made the suggested change.

4- Page 3 row 50: please add "the" before "current approaches".

Response: We have made the suggested change.

5- Page 3 rows 60 and 61: please modify "and 22 (61%) low-utilization (< 50%) of RA." To "and 22 departments (61%) with low-utilization (< 50%) of RA."

Response: We have made the suggested change.

6- Page 3 row 62: please correct "was" to "were".

Response: We have made the suggested change.

7- Page 4 row 70: please modify "Lipid emulsion is generally unavailable in China" to "Lipid emulsion is not widely available in China". This would be a better expression
of the fact you are presenting.

Response: We have made the suggested change.

8- Page 5 row 90: please add "Tab" to the first line of the paragraph.
Response: We have made the suggested change.

9- Page 5 row 90: please modify "Increases in the use of regional anesthesia (RA)" to "The increased use of regional anesthesia (RA)"
Response: We have made the suggested change.

10- Page 5 row 92: please modify "epidurals" to "epidural blocks".
Response: We have made the suggested change.

11- Page 5 row 94: please remove "however".
Response: We have made the suggested change.

12- Page 5 row 94: references [6-8] must be corrected to be [6, 7].
Response: We have made the suggested change.

13- Page 5 row 99: references [9, 10] must be corrected to be [8-10].
Response: We have made the suggested change.

14- Page 5: it is more appropriate to mention and discuss reference number [15] in the in background before mentioning it in the methods section.
Response: We have made the suggested change in line 107-108, page 5.

15- The section of the background is relatively short and did not present the following points:
- The presence of any previous data in china about the annual rate of peripheral nerve blocks or epidural blocks in china.
Response: Thanks for your insightful suggestions. Unfortunately, we did not find any recent official data about the annual rate of peripheral nerve blocks or epidural blocks in china. So we still cited the reference 1 in the section of the background.
- Why the author selected the field of orthopedic anesthesia only and did not include other fields as obstetric anesthesia or peripheral vascular surgeries (for example) to obtain a better idea about the availability and the incidence of the use of lipid emulsion rescue therapy in the treatment of local anesthetic systemic toxicity.
Response: Professor Xiangyang Guo, one of the corresponders for this article, was the
chairman of the orthopedic anesthesia group of the Chinese Society of Anesthesiology (CSA).

In order to get a better response rate, we selected the field of orthopedic anesthesia. We did not report incidents of local anesthetic toxicity with other fields as obstetric and peripheral vascular surgeries, in which lipid emulsion may be more available. However, orthopedic surgery in our study is the major indication for RA, with the utilization of PNBs in orthopedic surgery paralleling the increased number of ambulatory surgeries. We have explained this point in the section of discussion (Line 281-285, page 13).

16- Page 6 row 112: please add "Tab" to the first paragraph.

Response: We have made the suggested change.

17- Page 6 rows 114 and 115: please modify arrangement of references to be [12-15].

Response: We have made the suggested change.

18- Page 6 row 115: Please add the references after "the AAGBI and ASRA".[8, 9]

Response: We have made the suggested change.

19- Page 6 row 116: please modify "about current RA practices" to "about the current RA practices".

Response: We have made the suggested change.

20- Page 6: the first paragraph did not include the clinical trial registry of the study.

Response: We have added the Clinical Trial Registry number (ChiCTR-EOR-15006960) in line 113-115, page 6.

21- Page 6 row 123: please modify "indicated consent to study participation" to "indicated a consent to the study participation"

Response: We have made the suggested change.

22- Methods section is deficient in the following items:
- What is the 23 questions of the questionnaire?

Response: Thanks. The 23 item questionnaire has been added in in Appendix 1.

- The duration over which the questionnaire was applied is not cleared in the methods, i.e. what is the actual period did your study cover? Since you e-mailed the questionnaire or covered a certain period before that?

Response: The questionnaire consisted of 23 questions about the current RA practices and
the availability of lipid emulsions in 2013. We have specified this point in line 119, page 6.

- It is not clear why did you include only orthopedic patients? Did you include both epidural and peripheral nerve blocks or there were any sort of inclusion and exclusion criteria? Why other fields as obstetric or peripheral vascular surgeries were not included?

Response:

Yes, we include both epidural and peripheral nerve blocks. We have explained this in the legend of Table 1, “RA, regional anesthesia, includes peripheral nerve blocks, epidural and spinal blocks.”

In order to get a better response rate, we selected the field of orthopedic anesthesia only, since Professor Xiangyang Guo, one of the corresponders for this article, was the chairman of the orthopedic anesthesia group of the Chinese Society of Anesthesiology (CSA). Other fields as obstetric or peripheral vascular surgeries, will been further surveyed in the future study.

- What is the deadline to receive the feedback e-mails?

Response: December 1st, 2013 was the deadline to receive the feedback e-mails. We have added this point in line 125.

- Did you register the trial with any clinical trial registry?

Response: We have added the Clinical Trial Registry number (ChiCTR-EOR-15006960) in line 113-115, page 6.

23- Statistical analysis must be revised to provide the following points:

- What is the program did you use for statistical analysis and which version?

Response: All statistical analysis was performed with SPSS for Windows (version 16.0; SPSS, Chicago, IL). We have specified this in line 132-133, page 6.

- Page 6 row 127: you did not mention the names of the groups (that utilized more and less than 50% of RA. Although you mentioned them in the results, you should mention names of the groups in the methods first)

Response: Thanks for your insightful suggestions. As your kind advice, we have mentioned this in line 128-131, page 6.

- The section of statistics must be re-formatted.
Response: Thanks. The wording and sentence structure in the section of statistics have been carefully edited in line 128-134. Now it accurately conveys our intent.

24- Results:
- Page 7 row 133: please modify "from 36 of the 41 (88%)" to "from 36 out of the 41 (88%)"
Response: We have made the suggested change.
- Page 7 row 134: please modify "Of the 36 institutions," to "Out of the 36 institutions,"
Response: We have made the suggested change.
- Page 7 row 136: you mentioned intrathecal block and you did not comment on epidural block which is a major block in your survey?
Response: Please allow me to say sorry for the vague description of the RA in the last manuscript. RA included PNBs, epidural blocks and spinal anesthesia. We have specified this in line 140 and 437.
- The last sentence (rows 137, 138) need to be re-written to be clear to the reader or better placed in a table????
Response: As your kind advice, the distribution of the average number of PNBs performed monthly was shown in Table 2.
- Page 7 row 138: the phrase "performed > 60 PNBs per month"; did this the average over a certain year? Which year?
Response: Yes, it was the average in 2013. As your advice, the distribution of the average number of PNBs was shown in Table 2. We have specified these in the title of Table 2.

25- Table 1:
- The inter-quartile range should be written in the form of "2500-7200" and not "200, 7200"
Response: We have made the suggested change.
- Are you sure about the item hand and foot surgery or did you mean upper and lower limb surgeries? (please revise)
Response: Thanks. We have modified it to “Upper and lower limb surgeries” in Table 1 (Line 436).
- You mentioned in the last row of the table the intra-thecal and you did not mention the epidural or the neuro-axial blocks although this is the focus of the survey.

Response: Please allow me to say sorry again for the vague description of the RA in the last manuscript. RA included PNBs, epidural blocks and spinal anesthesia. We have specified this in line 140 and 437.

26- Page 7 row 140-142: you counted 37 institution while you received response from only 36 centers???

Response: We have checked the raw data, and revised it in line 143. Now there are 36 centers in total.

27- Figure 1: according to what you mentioned in page 7 row 143, 98% used two drugs (ropivacaine and bupivacaine), please revise your figure other drugs are presented for more than the remaining 2%??

Response: Because there were 5 (14%) responding departments selected multiple drugs as the preferred anesthetics, the summation of all percentages exceeded 100% (Figure 1). We have explained this point in line 144-147, page 7 in the revised manuscript.

28- Again in page 7 rows 148-151; you counted 38 centers while you received response from only 36 centers, please revise your data???

Response: We have checked the raw data, and revised it in line 156-158. Now there are 36 response centers in total. In addition, we also accordingly revised the figure 2.

29- The section RA practice (page 7 row 139-152): you did not mention any data about the number and percentage of epidural block or peripheral nerve block or the incidence of systemic toxicity, also you did not correlate between the technique used for the block (ultrasound guided or nerve stimulator guided...etc.) and the risk of systemic toxicity, this is an important outcome that you should present in your study.

Response:

We have added the description of percentage of RA (PNBs+epidural blocks+spinal anesthesia) in line 138-140 as following: Out of the 36 institutions, 14 (39%) used RA for orthopedic anesthesia in ≥ 50% of patients per year and 22 (61%) used RA for < 50% of these patients. RA included PNBs, epidural blocks and spinal anesthesia.

The lower use of ultrasound guidance and higher incidence of LAST in high-utilization
institutions may pointed to the clinical efficacy and safety of the performance of ultrasound-guided RA. Nevertheless, whether there is a negative correlation between use of ultrasound guidance and LAST in the present study need further research. We have explained this point in line 245-249 in the discussion.

30- Page 8 row 155: please modify "The distribution of LAST was" to "The distribution of LAST among techniques used was"

Response: We have made the suggested change.

31- Please insert corresponding references in rows 166-168.

Response: We have made the suggested change.

32- Page 9 row 193: please modify "poisoning" to "toxicity"

Response: We have made the suggested change.

33- Page 9 rows 193-196: please mention if you have any data about the use of electrical cardioversion and its relation to the use of lipid emulsion if any.

Response: We have added this point in line 208-210 as following: Unfortunately, no data about the use of electrical cardioversion and its relation to the use of lipid emulsion in this questionnaire.

34- Page 10 row 211: please modify "availability" to "non-availability" or "unavailability"

Response: Thanks. Indeed, some departments think there is no need to stock lipid emulsion in the department of anesthesiology since the emulsion has been stocked in the central pharmacy within the hospital. They mistakenly believe that they can get the lipid emulsion in time from the central pharmacy when the Local Anesthetic Systemic Toxicity occurred. So we respectfully think that "availability" should not change to "non-availability" or "unavailability".

35- Page 12 row 251: please insert reference after "AAGBI guidelines"

Response: We have made the suggested change.

36- Page 12 and 13 rows 260-271: please add to your limitations that you did not report incidents of local anesthetic toxicity with other fields as obstetric and peripheral vascular surgeries.
Response: We totally agree with you. We have made the suggested change in line 281-285.

37- The discussion is clear and satisfactory

Response: Thanks.

38- Page 19 row 414: you mentioned in the figure legend "in 2013" this gives an impression that the survey was applied for the year 2013 while you mentioned before that you asked institutions about incidents and LRT over last five years. Please clear this confusion and revise your data and the figure legend.

Response: Thanks. It was 2013, not the last five years We have revised the data and the figure legend.

39- Please revise the reference arrangement in the text (comment 18).

Response: We have made the suggested change.

We, again, thank you for your kind consideration of our manuscript and the comments and suggestions from these excellent reviewers. I would be happy to answer any further questions from you.

Sincerely,

Xiangyang Guo

Guo Xiangyang, MD, Ph.D, Department of Anesthesiology, Peking University Third Hospital, No. 49, North Garden Street, Haidian District, Beijing, 100191 China. Tel: 8610-82267276; E-mail: puthmzk@163.com.